AD_____

Award Number: W81XWH-08-2-0168

TITLE: The Relationship between Statins and Prostate Cancer Prevention

PRINCIPAL INVESTIGATOR: Wildon Farwell

CONTRACTING ORGANIZATION: Brigham and Women's Hospital, Inc.
Boston, MA 02115

REPORT DATE: September 2011

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
01-09-2011	Annual Summary	1 SEP 2008 - 31 AUG 2011

4. TITLE AND SUBTITLE
The Relationship between Statins and Prostate Cancer Prevention

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-08-2-0168

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Wildon Farwell

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Brigham and Women's Hospital, Inc.
Boston, MA 02115

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Prostate cancer is the most frequently diagnosed cancer among men in the United States, excluding non-melanoma skin cancer. Few risk factors and prevention strategies for prostate cancer are known. Some evidence suggests that statins, a class of medications that lower cholesterol, may reduce the incidence and progression of prostate cancer. Dr. Farwell obtained training that allowed him to investigate the relationship between statins and prostate cancer incidence and progression. He took classes at the Harvard School of Public Health and had regular research meetings with researchers at the Brigham and Women's Hospital and the VA Boston Healthcare System. He assembled datasets and performed analyses that examined the relationship between statins and total prostate cancer incidence as well as the incidence of both low and high grade prostate cancer.

15. SUBJECT TERMS
prostate cancer; statins; epidemiolog

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	40	19b. TELEPHONE NUMBER *(include area code)*

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Introduction

Prostate cancer is the most frequently diagnosed cancer, excluding non-melanoma skin cancer, in the United States. In 2011, it is estimated that 240,890 men will be diagnosed with prostate cancer and 33,720 men will die from prostate cancer. Few prevention strategies for prostate cancer exist. HMG-CoA reductase inhibitors, statins, may prevent prostate cancer incidence and progression. We previously reported that statin users were 10% less likely to develop any prostate cancer compared to users of anti-hypertensive medications. Other papers have reported that statin users are at decreased risk for any prostate cancer. However, these studies have primarily investigated the general relationship between statin use and total prostate cancer incidence and not the specific relationship between statin use and the grade of prostate cancer at diagnosis or prostate cancer progression. Therefore, we performed sophisticated analyses and I obtained additional training at the Harvard School of Public Health that enabled me to examine the specific relationship between statins and prostate cancer among men with various levels of risk for prostate cancer. Our studies will investigated the relationship between statin use and prostate cancer grade at diagnosis and prostate cancer progression using data from the Physicians' Health Study and VA New England Healthcare System.

Body

I met regularly with researchers at both Brigham and Women's Hospital and the VA Boston Healthcare System. I met regularly with my primary mentor, J. Michael Gaziano, MD MPH. During these meetings, Dr. Gaziano and I discussed current research findings and opportunities for new research. We also attend regular research meetings at the VA Boston Healthcare System. At these research meetings, current research projects in the VA Healthcare System were discussed. I strengthened my research ties with the Massachusetts Veterans Epidemiology Research and Information Center at the VA Boston Healthcare System. I worked with several investigators such as Drs. Leonard D'Avolio, PhD, and Elizabeth V. Lawler, ScD MPH, on projects related to prostate cancer incidence and progression.

I performed analyses of data from the Physicians' Health Study (PHS) II, Appendix 2. In brief, I examined the relationship between ever taking a cholesterol lowering medication and the incidence of prostate cancer. I also examined the relationship between cholesterol and prostate cancer incidence. In both analyses, I attempted to control for multiple confounders including comorbid conditions. After performing multiple analyses, I was not able to find a convincing relationship between statins and prostate cancer incidence. The p-value for a hazard ratio for a history of cholesterol lowering medication use and current cholesterol medication use was 0.16 and 0.56, respectively. I was also not able to find a convincing relationship between cholesterol and prostate cancer incidence. The p-value for a test of trend across quartiles of cholesterol was 0.9062. Because these results were inconclusive, we have decided not to publish our findings at this time.

I published my findings from the VA New England Healthcare System, Appendix 3. In brief, I used electronic and administrative files to identify 55,875 men who were either taking a statin or antihypertensive medication and were routine users of the VA New England Healthcare System. I then created age- and multivariate-adjusted Cox proportional hazard models to calculate the hazard ratio (HR), 95% confidence interval (CI), for prostate cancer incidence among patients taking statins compared to patients taking antihypertensive medications. I also grouped patients taking statins into categories of equivalent simvastatin dosages and then compared these groups to patients taking antihypertensive medications for the incidence of prostate cancer. Furthermore, I performed similar

analyses examining the relationship between using statins compared to antihypertensive medications for the incidence of low-grade and high-grade prostate cancer. Low-grade prostate cancer was defined as a Gleason score of ≤ 7 (3+4) at biopsy and high-grade prostate cancer was defined as a Gleason score of ≥ 7 (4+3) at biopsy.

Compared to men taking an antihypertensive medication, men taking a statin were 30% less likely to be diagnosed with prostate cancer, Table 2. Furthermore, statin users were 13% less likely to be diagnosed with low-grade prostate cancer but 60% less likely to be diagnosed with high-grade prostate cancer. A dose response for prostate cancer incidence was also identified with an increased dose of statin associated with a decreased risk for prostate cancer and high-grade prostate cancer. A paper describing these results was published in the *Journal of the National Cancer Institute*.

Table 2. Multivariate * adjusted hazard ratios (95% confidence interval) for total prostate cancer, low grade prostate cancer, and high grade prostate cancer by statin use and categories of equivalent simvastatin doses.

		Categories of Equivalent Simvastatin Doses			
	Statin	0 mg	1-10 mg	11 – 19 mg	≥ 20 mg
Prostate Cancer	0.70 (0.53, 0.91)	Referent	0.68 (0.52, 0.91)	0.68 (0.50, 0.92)	0.66 (0.46, 0.96)
Gleason Score ≤ 7 (3+4)	0.87 (0.63, 1.21)	Referent	0.82 (0.59, 1.13)	0.78 (0.55, 1.12)	0.86 (0.57, 1.30)
Gleason Score ≥ 7 (4+3)	0.40 (0.25, 0.65)	Referent	0.43 (0.25, 0.74)	0.48 (0.27, 0.87)	0.28 (0.11, 0.67)

* Multivariate adjusted models were adjusted for the following variables: statin use (yes, no), finasteride use history (yes, no), age (years), serum total cholesterol (mg/dL), race (white, black, other, missing), smoking history (yes, no), aspirin use (yes, no), heart disease (yes, no), diabetes mellitus (yes, no), history of PSA test (yes, no)

I am awaiting additional mortality data to complete his analysis in the Early Stage Prostate Cancer Cohort on the relationship between statin use and mortality among men diagnosed with early stage prostate cancer. My preliminary analyses to date indicate that statins may be associated with decreased risk for prostate cancer related mortality among men who are diagnosed with early stage prostate cancer.

In addition, I also published on the relationship between height and prostate cancer grade among men diagnosed with early stage prostate cancer, Appendix 4. In brief, I performed logistic regression to calculate the odds ratio (OR), 95% confidence interval (CI), for the association between height and prostate cancer grade at diagnosis. I found that taller men were more likely to be diagnosed with high

grade prostate cancer, OR 1.11 (95% CI 0.96, 1.29). In addition, taller diabetic men, OR 1.35 (95% CI 1.00, 1.81), and African-American men, OR 1.44 (95% CI 1.06, 1.95), were particularly more likely to be diagnosed with high grade prostate cancer. A paper describing these results has been published in *Cancer Causes and Control*.

Key Research Accomplishments

a) Paper published in the Journal of the National Cancer Institute describing the results of the analysis in the New England Healthcare System. We found that statin use was associated with a 30% risk reduction in prostate cancer and a 13% risk reduction in low-grade prostate cancer and 60% risk reduction in high-grade prostate cancer.
b) Paper published in Cancer Causes and Control describing the results of an analysis in the Early Stage Prostate Cancer Cohort. We found that height was associated with high-grade prostate cancer. In particular, taller diabetic men and African-American men were particularly more likely to be diagnosed with high-grade prostate cancer. Although this analysis was not outlined in my original statement of work, it is a related topic using a dataset described in my proposal.
c) Presented results from my analyses in the VA New England Healthcare System at IMPaCT in Orlando, FL, in March, 2011.

Reportable Outcomes

The third and final year of my research training award was dedicated to analyzing datasets from the Physicians' Health Study and publishing results from datasets of the VA New England Healthcare System, and Early Stage Prostate Cancer Cohort Study. I presented an oral abstract and poster at IMPaCT from work I did with data from the VA New England Healthcare System.

Conclusion

During the third and final year of the Physician Research Training Award, I left full-time employment at the VA Boston Healthcare System and Brigham and Women's Hospital and am now fully employed at Biogen Idec, a pharmaceutical company. However, I completed two manuscripts and published these in addition to continuing to explore the relationship between statins, cholesterol and prostate cancer in the Physicians' Health Study and Early Stage Prostate Cancer Cohort study.

Prostate cancer is commonly diagnosed and prevention strategies for prostate cancer incidence and progression are needed. Statins may be a safe and effective treatment for prostate cancer prevention. I believe the results of my studies contributed to better understanding the risk factors for high-grade prostate cancer and a possible prevention strategy for high-grade prostate cancer. The training that I obtained during this grant will help me develop new treatments for multiple potential indications in my new role at a pharmaceutical company.

Appendix 1: CV of Dr. Wildon R. Farwell, MD MPH

Harvard Medical School/Harvard School of Dental Medicine
Curriculum Vitae

Date Prepared:	**11 September 2011**
Name:	**Wildon R. Farwell, MD MPH**
Office Address:	**VA Boston Healthcare System** **MAVERIC** **150 S. Huntington Avenue** **Boston, MA 02130** **Brigham and Women's Hospital** **Division of Aging** **1620 Tremont Street** **Boston, MA 02120**
Home Address:	**6 Glezen Lane** **Wayland, MA 01778**
Work Phone:	**VA: 857-364-4201** **BWH: 617-278-0785**
Work Email:	**VA: wildon.farwell@va.gov** **BWH: wfarwell@partners.org**
Work FAX:	VA: 857-364-4424 BWH: 617-525-7739
Place of Birth:	Springfield, MO; USA

Education

1996	BS (Magna cum laude)	Biology	University of Missouri-Columbia, Columbia, MO
2000	MD	Medicine	University of Missouri-Columbia School of Medicine, Columbia, MO
2005	MPH	Clinical Effectiveness	Harvard School of Public Health, Boston, MA

Postdoctoral Training

7/2000 - 6/2003	Resident	Internal Medicine	Indiana University, Indianapolis, IN

7/2003 - 6/2006	Fellow	General Internal Medicine	Harvard Medical School, Boston, MA

Faculty Academic Appointments

2006 - 2010	Instructor	Medicine	Harvard Medical School, Boston, MA
2010 -	Assistant Professor	Medicine	Harvard Medical School, Boston, MA

Appointments at Hospitals/Affiliated Institutions

July, 2003 - 2007	Associate Physician	Medicine (Aging)	Brigham and Women's Hospital, Boston, MA
July, 2004 - 2007	Courtesy Medical Staff	Medicine	Faulkner Hospital, Boston, MA
July, 2007 -	Staff Physician	Medicine (General Medicine)	VA Boston Healthcare System, Boston, MA
July, 2007 -	Associate Epidemiologist	Medicine (Aging)	Brigham and Women's Hospital, Boston, MA
June, 2010 -	Adjunct Instructor of Medicine	Medicine	Boston University School of Medicine, Boston, MA

Major Administrative Leadership Positions

Local

2007 -	Associate Director, Harvard Medical School Fellowship in General Medicine and Primary Care at the VA Boston Healthcare System	VA Boston Healthcare System, Boston, MA

Committee Service

Local

1998-2000	Admissions Committee, Member	University of Missouri-Columbia, School of Medicine, Columbia, MO
2007-	Institutional Review Board, Member	VA Boston Healthcare System, Boston, MA

National and International

2003-2005	Residency Review Committee for Internal Medicine, Member	Accreditation Council for Graduate Medical Education
2010-	Executive Committee for CSP 572: Genetics of Functional Disability in Schizophrenia and Bipolar Illness	VA Healthcare System

Professional Societies

2000-	American College of Physicians	Member
	2003	President, Indiana Council of Associates
2002-	Society of General Internal Medicine	Member
	2005-2006	Member, National Meeting Programming Committee
	2006-2007	Member, Abstract Review Committee
	2007-	Member, Finance Committee

Editorial Activities

Ad Hoc Reviewer, Archives of Internal Medicine
European Journal of Epidemiology
Clinical Endocrinology
Diabetes Care

Other Editorial Roles

2009 - Editorial Board — Open Journal of Oncology

Honors and Prizes

1997	Student Leadership and Service Award	University of Missouri-Columbia, School of Medicine	
2000	Holt Leadership Award	University of Missouri-Columbia, School of Medicine	
2000	Commencement Speaker	University of Missouri-Columbia, School of Medicine	
2007	Joseph E. Johnson Leadership Award	American College of Physicians	This national award recognizes an Associate member of the College who has demonstrated qualities that exemplify the College's mission "to enhance the quality and effectiveness of health care by fostering excellence and professionalism in the practice of medicine."
2009	Elected to Fellow	American College of Physicians	

Report of Funded and Unfunded Projects

Funding Information

Past

2006-2009 Head and Neck Cancer Treatment in the Veterans Affairs (VA): Evaluation of Treatment Patterns, Outcomes, and Costs

Pharmerit
Co-Investigator
This pharmacoepidemiology project was designed to describe treatment patterns for patients with locoregionally advanced squamous cell cancer of the head and neck. I oversaw the data collection and analysis and I wrote the paper reporting our findings.

2007-2009 Testosterone Supplementation for Men with Sarcopenia
NIH, U01AGO14369/CFDA
Site-PI, $100,000
This randomized controlled clinical trial was designed to investigate whether testosterone gel could increase muscle strength among men with sarcopenia and low testosterone.

2007-2009 VISN Collaborative for Improving Hypertension Management with ATHENA-HTN
VA
Site-PI, $91,000
This randomized controlled trial was designed to investigate whether a computerized tool would help primary care providers manage patients with hypertension.

2009 The Association between Statins and Melanoma Recurrence
Carter Foundation
Co-Investigator, $30,000
The major goal of this study was to develop a cohort of patients with melanoma. The project investigated the relationship between medications to lower cholesterol and melanoma incidence and progression.

2009 The Study of Heart and Renal Protection
Merck, MK-0653
Site-PI, $30,000
This international randomized controlled clinical trial was designed to investigate whether cholesterol lowering treatments reduced cardiovascular outcomes among patients with renal disease.

Current

2008-2011 The Relationship between Statins and Prostate Cancer
DoD, PC073416
PI, $390,000
The major goal of this study is to develop skills to be an independent successful researcher. The projects will investigate the relationship between medications to lower cholesterol and prostate cancer incidence and progression.

Report of Local Teaching and Training

Teaching of Students in Courses

2003	Clinical Epidemiology (AC701.0) 2nd year medical students	Harvard Medical School, Boston, MA Tutor for a 2-hr session per week for 4 months
2004-2006	Epidemiology 242 MPH students	Harvard School of Public Health, Boston, MA Teaching Assistant for a 90 minute session per week for 4 months
2004-2007	Preventive Medicine and Nutrition (PM711.0) 2nd year medical students	Harvard Medical School, Boston, MA Tutor for a 2-hr session per week for 4 months
2009-	Measuring and Analyzing the Outcomes of Health Care (HPM 530) MPH students	Harvard School of Public Health, Boston, MA Lecturer for a 120 minute session
2009	Introduction to Epidemiology (EP 711 A1) MPH students	Boston University School of Public Health, Boston, MA Lecturer for a 60 minute session
2010	Patient Doctor II (IN761.14) 2nd year medical students	Harvard Medical School, Boston, MA Faculty for a 120 minute session

Clinical Supervisory and Training Responsibilities

2004-2005	Primary Care Clinic Preceptor	4 hours per week
2005	General Medicine Ward Attending	8 hours per day for 2 weeks per year
2006-	Adult Diagnostic Treatment Center Preceptor	8 hours per day for 2 months per year

Formal Teaching of Peers (e.g., CME and other continuing education courses)

No presentations below were sponsored by outside entities

2008	Screening for Prostate Cancer A Core Curriculum in Adult Primary Care Medicine, Boston University	Single Presentation Boston University School of Medicine, Boston, MA

Local Invited Presentations

No presentations below were sponsored by outside entities

2007	PSA Testing for Prostate Cancer; Grand Rounds Department of Medicine, VA Boston Healthcare System, Boston, MA

Report of Regional, National and International Invited Teaching and Presentations

Invited Presentations and Courses

Regional

No presentations below were sponsored by outside entities

2007 After a period of intense debate, are physicians ordering PSA tests more frequently? ; Presenting author (selected abstract)
Boston, MA (Society of General Internal Medicine)

2008 Is High-Density-Lipoprotein Cholesterol Associated with Developing Prostate Cancer?; Presenting author (selected abstract)
Boston, MA (Society of General Internal Medicine)

2008 Career Panel; Panelist (selected presenter)
Boston, MA (Society of General Internal Medicine)

National

No presentations below were sponsored by outside entities

2003 Resident's Perspective on Professionalism; Presenter
New Orleans, LA (Accreditation Council for Graduate Medical Education)

2004 Mistakes Residents Notice; Presenter
Chicago, IL (Accreditation Council for Graduate Medical Education)

2004 Student, Resident, and Fellow Career Development Workshop; Presenter
Chicago, IL (Society of General Internal Medicine)

2004 Making things simpler: can non-HDL predict MI as well as LDL-C?; Presenter
St. Louis, IL (Washington University)

2005 Making things simpler: can non-HDL predict MI as well as LDL-C?; Presenter
Pittsburgh, PA (University of Pittsburgh)

2007 The Relationship between Statins and Cancer Incidence in a Veterans Population; Presenter
Huntington Beach, CA (Southwest Oncology Group, Melanoma Prevention Working Group)

2009 Pharmacoepidemiology in the VA and Beyond; Presenter (Selected Abstract)
Miami, FL (Society of General Internal Medicine)

International

No presentations below were sponsored by outside entities

2010 The principles and pitfalls of working with large administrative databases such as in the Department of Veterans Affairs; Presenter
Boston, MA (Harvard School of Public Health, Center for Continuing Professional Education, Measurement, Design, and Analysis Methods for Outcomes Research)

Report of Clinical Activities and Innovations

Current Licensure and Certification

2000 - Medical License
2000 - 2003 Indiana
2003 - Massachusetts

2004 - American Board of Internal Medicine

Practice Activities

July 2003 - June 2006	Clinician	Preventive Cardiology, VA Boston Healthcare System, Boston, MA	4 hours per week
July 2006 -	Clinician	Primary Care, VA Boston Healthcare System, Boston, MA	4 hours per week

Report of Education of Patients and Service to the Community

Activities

No activities below were sponsored by outside entities

2009 American Friends of Kenya / Physician
I participated in a medical mission with a total of 5 physicians that saw over 900 patients in and around Nairobi, Kenya, over a period of 6 days.

Report of Scholarship

Publications

Peer reviewed publications in print or other media

Research Investigations

1. **Farwell W**, Simonyi A, Scott H, Zhang JP, Carruthers V, Madsen R, Johnson J, Sun GY. Effects of ischemic tolerance on mRNA levels of IP3RI, β-actin, and neuron-specific enolase in hippocampal CA1 area of the gerbil brain. Neurochemical Research. 1998;23(4): 539-42.

2. **Farwell WR**, Stump TE, Wang J, Tafesse E, L'Italien G, Tierney WM. Weight Gain and New Onset Diabetes Associated with Olanzapine and Risperidone. JGIM. 2004;19(12): 1200-5.

3. **Farwell WR**, Sesso HD, Buring JE, Gaziano JM. Non-high density lipoprotein cholesterol versus low density lipoprotein cholesterol as a risk factor for first nonfatal myocardial infarction. Am J Cardiol 2005;96(8):1129-1134.

4. Taylor EN, Forman JP, **Farwell WR**. Serum anion gap and blood pressure in the National Health and Nutrition Examination Survey. Hypertension. 2007;50:1-5.

5. **Farwell WR**, Linder JA, Jha AK. Trends in Prostate-Specific Antigen Testing From 1995 Through 2004. Arch Intern Med. 2007;167(22):2497-2502.

6. **Farwell WR**, Scranton RE, Lawler EV, Lew RA, Brophy MT, Fiore LD, Gaziano JM. The Association between Statins and Cancer Incidence in a Veterans Population. J Natl Cancer Inst. 2008;100:134-139.

7. **Farwell WR**, Gaziano JM, Norkus EP, Sesso HD. The relationship between total plasma carotenoids and risk factors for chronic disease among middle-aged and older men. Br J Nutr. 2008;12:1-7.

8. **Farwell WR**, Taylor EN. Serum Bicarbonate, Anion Gap, and Insulin Resistance in the National Health and Nutrition Examination Survey. Diabet Med. 2008;25:798-804.

9. Scranton RE, **Farwell WR**, Gaziano JM. Lack of cholesterol awareness among physicians who smoke. Int J Environ Res Public Health. 2009;6:635-642.

10. Hernandez RK, **Farwell WR**, Canton MD, Lawler EV. Cholinesterase inhibitors and incidence of bradycardia among dementia patients in the Veterans Affairs New England Healthcare System. J Am Geriatr Soc. 2009;57:1997-2003.

11. Chen LM, **Farwell WR**, Jha AK. Primary care visit duration and quality: does good care take longer? Arch Intern Med. 2009;169(20):1866-1872.

12. **Farwell WR**, Taylor EN. Serum Anion Gap, Bicarbonate, and Inflammatory Biomarkers in the National Health and Nutrition Examination Survey. CMAJ. 2009; DOI:10.1503/cmaj.090329

13. Basaria S, Coviello AD, Travison TG, Storer TW, **Farwell WR**, Jette AM, Eder R, Tennstedt S, Ulloor J, Zhang A, Choong K, Lakshman KM, Mazer NA, Miciek R, Krasnoff J, Elmi A, Knapp PE, Brooks B, Appleman E, Aggarwal S, Bhasin G, Hede-Brierley L, Bhatia A, Collins L, LeBrasseur N, Fiore LD, Bhasin S. Adverse events associated with testosterone administration in a randomized trial. N Engl J Med. 2010; DOI:10.1056/NEJMoa1000485

14. D'Avolio L, **Farwell WR**, Nguyen T, Chen Y, Harris O, Fiore LD. Evaluation of a generalizable approach to clinical information retrieval using the automated retrieval console (ARC). J Am Med Inform Assoc. JAMIA. 2010;17:375-382.

15. Shargorodsky J, Curhan GC, **Farwell WR**. Prevalence and characteristics of tinnitus among US adults. Am J Med. 2010;123:711-718.

16. Gutierrez OM, **Farwell WR**, Kermah D, Taylor EN. Racial difference in the relationship between vitamin D, bone mineral density, and parathyroid hormone in the National Health and Nutrition Examination Survey. Osteoporosis Int. 2011;22(6):1745-1753.

17. D'Avolio LW, **Farwell WR**, Fiore LD. Comparative effectiveness research and medical informatics. Am J Med. 2010;123(12 Suppl 1):e32-37.

18. **Farwell WR**, D'Avolio LW, Scranton RE, Lawler EV, Gaziano JM. Statins and prostate cancer diagnosis and grade in a veterans population. J Natl Cancer Inst. 2011;103(11):885-892.

19. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. Lancet. 2011;377(9784):2181-2192.

20. Travison TG, Basaria S, Storer TW, et al. Clinical meaningfulness of the changes in muscle performance and physical function associated with testosterone administration in older men with mobility limitation. J Gerontol A Biol Sci Med Sci. 2011; DOI: 10.1093/gerona/glr100

21. **Farwell WR**, Lourenco C, Holmberg E, Hall RB, D'Avolio L, Lawer LV, Gaziano JM. The association between height and prostate cancer grade in the Early Stage Prostate Cancer Cohort Study. Cancer Causes Control. 2011; DOI: 10.1007/s10552-011-9820-x

Non-peer reviewed scientific or medical publications/materials in print or other media

Reviews

1. Rahilly CR, **Farwell WR**. Prevalence of smoking in the United States: a focus on age, sex, ethnicity, and geographic patterns. Current Cardiovascular Risk Reports. 2007;1(5):379-383.

Letter to the Editor

1. **Farwell WR**, Scranton RE, Lawler EV, Lew RA, Brophy MT, Fiore LD, Gaziano JM. Response: Re: The Association Between Statins and Cancer Incidence in a Veterans Population. J Natl Cancer Inst. 2008;100:973-974.

Abstracts, Poster Presentations and Exhibits Presented at Professional Meetings

1. **Farwell WR**, Sesso HD, Lew RA, Scranton RE, Gaziano JM. The Association Between Statins and Cancer Prevention in the Physicians' Health Study. Presented at the Society of General Internal Medicine New England Region and National Meetings, 2006 meetings

2. **Farwell WR**, Scranton RE, Lawler EV, Lew RA, Gaziano JM. Can Statins Prevent Lung Cancer? Presented at the Society of General Internal Medicine New England Region, 2007 meeting; Presented at the Society of General Internal Medicine, 2007 national meeting

3. **Farwell WR**, Scranton RE, Lawler EV, Lew RA, Gaziano JM. Can Statins Prevent Colorectal Cancer? Presented at the Society for Epidemiologic Research, 2007 national meeting

4. Scranton RE, **Farwell W**, Ezrokhi M, Gaziano JM, Cincotta AH. Quick release bromocriptine (Cycloset ™) improves glycaemic control in patients with diabetes failing metformin/sulfonylurea combination therapy. Presented at the European Association for the Study of Diabetes, 2007 international meeting

5. **Farwell WR**, Sesso HD, Gaziano JM. Is high-density-lipoprotein cholesterol associated with the

risk of developing prostate cancer? Presented at the Society of General Internal Medicine New England Region, 2008 meeting; Presented at the Society of General Internal Medicine, 2008 national meeting

6. **Farwell WR**, Lawler E, Boulanger L, Cincotta AH, Scranton RE. Assessment of safety for bromocriptine: comparisons of reporting systems and a retrospective cohort study. Presented at the International Society for Pharmacoeconomics and Outcome Research, 2008 international meeting

7. Lawler E, Chittamooru S, Botteman M, **Farwell W**. Locally Advanced Head and Neck Cancer Treatment Patterns. Presented at the American Academy of Otolaryngology - Head and Neck Surgery, 2008 national meeting

8. Clark AS, **Farwell WR**. Height and Breast Cancer Mortality. Presented at Boston University School of Medicine Research Day, May 2008

9. Scranton RE, **Farwell WR**, Ezrokhi M, Gaziano JM, Cincotta AH. Quick Release Bromocriptine (Cycloset TM) A Novel Treatment for Type 2 Diabetes also Demonstrates Improvements in Blood Pressure. Presented at the International Diabetes Federation, October 2009

10. Paik JM, **Farwell WR**, Taylor EN. Determinants of plasma parathyroid hormone levels in the National Health and Nutrition Examination Survey. Accepted for presentation at the American Society of Bone and Mineral Research, October 2010

11. **Farwell W**, D'Avolio L, Scranton R, Lawler E, Gaziano JM. Are statins associated with decreased risk for prostate cancer diagnosis and grade? Accepted for presentation at Innovative Minds in Prostate Cancer Today, March 2011

Appendix 2: Analysis plan to explore the relationship between taking lipid modifying treatment and prostate cancer in the Physicians' Health Study

DATA SET REQUEST -- PC SAS FORMAT

To: Vadim Bubes; phsrequest@rics.bwh.harvard.edu
From: Wildon R. Farwell, MD MPH
cc: J. Michael Gaziano, MD MPH; Howard D. Sesso, ScD MPH

Lipid Modifying Treatments and Prostate Cancer

Creation of Baseline Population

PHS II cohort
No pre-randomization cancer, prostate cancer

Outcome Variable

(1) Total Cancer
(2) All Forms of Cancer, each listed seperately
    Censor variable (n/y)
    Time to censor (years)
(3) For Prostate Cancer Specifically,
    Clinical Stage at Diagnosis
    Gleason Scores

Exposure Variables

(1) Lipid Modifying Treatments
Enrollment Questionnaire: Self reported treatment: "Are you currently being treated with any cholesterol-lowering medications? (n/y)"
    Statin
    Nonstatin
Follow-up Questionnaires: "Are you currently taking medications specifically for the following conditions, hypercholesterolemia? (n/y)"

(2) Hypertension
Enrollment Questionnaire: Self reported treatment: "Are you currently being treated with any medications specifically for hypertension?"
Follow-up Questionnaire: "Are you currently taking medications specifically for the following conditions, hypertension? (n/y)"

Baseline Co-Variates (PHS Cohort and PHS II Old Doc Enrollment Questionnaires)

Demographics
Age (years)
Weight (lbs.)
BMI (kg/m^2)

Social
Smoking (never, former, current; number/day)
Alcohol use (6+/day, 4-5/day, 2-3/day, 1/day, 5-6/week, 2-4/week, 1/week, 1-3/month, rarely/never)
Exercise (daily, 5-6/week, 2-4/week, 1/week, 1-3/month, rarely/never)

Family Hx
Prostate cancer (n/y/unknown; age at diagnosis)
Colon or rectal cancer (n/y/unknown; age at diagnosis)

Other cancer (n/y/unknown; age at diagnosis)
MI (n/y/unknown; age at diagnosis)

Co-morbid conditions
Hypertension (self-reported; SBP, DBP)
Hypercholesterolemia (self-reported; total cholesterol, HDL cholesterol)
MI (n/y)
Stroke (n/y)
PTCA (n/y)
Angina (n/y)
CABG (n/y)
Diabetes mellitus (n/y)
TIA (n/y)
Carotid artery surgery (n/y)
Other peripheral artery surgery (n/y)
Abdominal aortic aneurysm (n/y)
Benign prostatic hyperplasia (n/y; mm/yyyy)
Benign prostatic hyperplasia surgery (n/y; mm/yyyy)
Vasectomy (n/y; mm/yyyy)
Prostatitis (n/y; mm/yyyy)
Prostatic infection (n/y; mm/yyyy)

Thanks for your help,

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Appendix 3: Published Paper from the VA New England Healthcare System Titled, "The Relationship Between Statins and Prostate Cancer Diagnosis and Grade Among Veterans in the New England VA Healthcare System."

DOI: 10.1093/jnci/djr108
Advance Access publication on April 15, 2011.

ARTICLE

Statins and Prostate Cancer Diagnosis and Grade in a Veterans Population

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Manuscript received September 29, 2010; revised February 2, 2011; accepted February 25, 2011.

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Background Although prostate cancer is commonly diagnosed, few risk factors for high-grade prostate cancer are known and few prevention strategies exist. Statins have been proposed as a possible treatment to prevent prostate cancer.

Methods Using electronic and administrative files from the Veterans Affairs New England Healthcare System, we identified 55 875 men taking either a statin or antihypertensive medication. We used age- and multivariable-adjusted Cox proportional hazard models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for prostate cancer incidence among patients taking statins (n = 41 078) compared with patients taking antihypertensive medications (n = 14 797). We performed similar analyses for all lipid parameters including total cholesterol examining each lipid parameter as a continuous variable and by quartiles. All statistical tests were two-sided.

Results Compared with men taking an antihypertensive medication, statin users were 31% less likely (HR = 0.69, 95% CI = 0.52 to 0.90) to be diagnosed with prostate cancer. Furthermore, statin users were 14% less likely (HR = 0.86, 95% CI = 0.62 to 1.20) to be diagnosed with low-grade prostate cancer and 60% less likely (HR = 0.40, 95% CI = 0.24 to 0.65) to be diagnosed with high-grade prostate cancer compared with antihypertensive medication users. Increased levels of total cholesterol were also associated with both total (HR = 1.02, 95% CI = 1.00 to 1.05) and high-grade (HR = 1.06, 95% CI = 1.02 to 1.10) prostate cancer incidence but not with low-grade prostate cancer incidence (HR = 1.01, 95% CI = 0.98 to 1.04).

Conclusions Statin use is associated with statistically significantly reduced risk for total and high-grade prostate cancer, and increased levels of serum cholesterol are associated with higher risk for total and high-grade prostate cancer. These findings indicate that clinical trials of statins for prostate cancer prevention are warranted.

J Natl Cancer Inst 2011;103:885–892

In 2010, it is estimated that 217 730 men will be diagnosed with prostate cancer and 32 050 men will die of prostate cancer (1). Prostate cancer is the most commonly diagnosed cancer among men, excluding nonmelanoma skin cancer, and is the second most common cause of cancer-related mortality (1). Although prostate cancer is prevalent and a common cause of cancer-related mortality, few prevention strategies for prostate cancer currently exist.

One potential prevention strategy for prostate cancer is taking a statin, 3-hydroxy-3-methyl-glutaryl-coenzyme reductase inhibitor. Several recent published studies have reported that statin use may be associated with a decreased risk for advanced prostate cancer (2–5). Platz et al. (2) found a statistically significant inverse relationship between statins and metastatic prostate cancer. Other studies (3–5) have shown that statin use was associated with a decreased Gleason score at prostate cancer diagnosis. However, most recently, one study (6) did not find that statin use was associated with decreased risk for advanced prostate cancer. Unfortunately, a limitation of several of these studies is the potential healthy user bias (7,8). Compared with nonusers, patients who use statins may have a different risk profile for prostate cancer. For example, statin users may have different access to health care, including use of preventive health services such as prostate-specific antigen (PSA) testing (8,9); different competing risks; and different diet and exercise habits compared with nonusers. This bias may result in statin users appearing to have a decreased risk for advanced prostate cancer when in fact something else that is associated with statin use and different from the comparison population may be responsible for the decrease in risk.

A recent study has shown that low serum cholesterol is associated with a decreased risk for advanced prostate cancer compared with high serum cholesterol (10). Platz et al. (10) found a statistically significant direct relationship between higher levels of serum cholesterol and increased risk for high-grade prostate cancer, which supports the hypothesis that taking a medicine to lower cholesterol levels may prevent advanced prostate cancer. However, several questions remain about the relationship between statins,

CONTEXT AND CAVEATS

Prior knowledge

The association between statin use and the prevention of prostate cancer is unclear.

Study design

The electronic and administrative files of a large cohort of men taking a statin or antihypertensive medication were obtained from the Veterans Affairs New England Healthcare System. Prostate cancer incidence among these two patient populations was compared.

Contribution

Statin use was associated with a lower risk of total and high-grade prostate cancer. Increased serum cholesterol levels were associated with an increased risk for total and high-grade prostate cancer.

Implications

Further studies should be done to investigate the role of cholesterol in high-grade prostate cancer. Statins are a potential preventive therapy for prostate cancer and should be investigated in clinical trials.

Limitations

There are few reports of an association between serum cholesterol and prostate cancer incidence; further studies are necessary to confirm these results. It is unknown if and how often patients took their medications.

From the Editors

cholesterol, and prostate cancer. After attempting to control for a potential healthy user bias, is statin use associated with decreased incidence of high-grade prostate cancer? Is there a dose response between statins and the incidence of high-grade prostate cancer? Are lipid parameters such as high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and non-HDL-C associated with the incidence of high-grade prostate cancer or is total cholesterol (TC) alone associated with the incidence of high-grade prostate cancer? Therefore, we built on our previously published analysis of statins and cancer diagnosis to specifically examine the relationship between statins and pathology-confirmed prostate cancer diagnosis and grade. Furthermore, we examined the relationship between several different lipid parameters and pathology-confirmed prostate cancer diagnosis and grade.

Methods

Data Source and Definition of Outcome

We assembled a retrospective cohort of male patients aged 18 years and older in the Veterans Affairs (VA) New England Healthcare System between January 1, 1997, and December 31, 2007, using national and regional databases. The study protocol was reviewed and approved by the Institutional Review Board of the VA Boston Healthcare System, and the board granted our study a waiver from obtaining informed consent from the patients. We obtained patient level data from the VA National Patient Care Database and the VA Pharmacy Benefits Management System. Patient level data captured in the VA national database system include both inpatient and outpatient demographic characteristics, visits, diagnoses, procedures, medications, and laboratory test results. We defined the cohort entry date as the first recorded prescription fill date for the medication of interest. All patients with a cancer diagnosis were defined by *International Classification of Diseases* (*ICD*) codes. *ICD-Ninth Revision*, *Clinical Modification* (*ICD-9-CM*) codes 140.XX–208.XX or VA pathology-confirmed prostate cancer diagnosis, on or before the cohort entry date, were excluded from the study analyses. An observation period for each patient was defined as beginning 2 years after their entry date and continuing until 1) the first occurrence of a diagnosis of prostate cancer; 2) an *ICD-9-CM* code for a cancer other than prostate cancer or nonmelanoma skin cancer; 3) 1 year after the last fill date for a medication of interest; 4) death; or 5) the end of the cohort, December 31, 2007. To diminish any potential effects of latent cancer on our predictor variables, we excluded patients that were diagnosed with cancer within 2 years after their potential entry date. Because long-term exposure would likely be required for any medication to reduce prostate cancer incidence, we also excluded all patients who discontinued their medication of interest within 2 years after their potential entry date.

The primary outcomes of our analyses were prostate cancer incidence and Gleason grade. Patients with prostate cancer and the corresponding Gleason grade of their tumors were identified in the electronic medical record of the VA New England Healthcare System using the Automated Retrieval Console (11). Briefly, from a dataset of patients with an *ICD-9-CM* code for prostate cancer, Automated Retrieval Console identified pathology reports consistent with prostate cancer. Automated Retrieval Console was able to separate reports consistent with a biopsy from reports consistent a prostatectomy. We then used natural language processing to identify Gleason grade within these reports. If we identified a pathology report consistent with prostate cancer, we defined that patient as having been diagnosed with prostate cancer on the date of the pathology report. We further stratified our outcome by high- and low-grade prostate cancer. Low-grade prostate cancer was defined as a total Gleason score of less than or equal to 7 (3 + 4), and high-grade prostate cancer was defined as a total Gleason score of greater than or equal to 7 (4 + 3). Our method of identifying prostate cancer grade was found to have 97% recall and 95% precision (11).

Predictor Variables

Patients were selected among active users of the VA New England Healthcare System who 1) filled at least two prescriptions (generally a 90-day supply) for any antihypertensive medication or statin within 1 year, 2) continued filling at least yearly prescriptions for an identified medication of interest, and 3) were seen at least once per year in an outpatient VA clinic. Antihypertensive medication users were defined as patients who never filled a prescription for any cholesterol-lowering medication but filled prescriptions from the following classes of antihypertensive medications: beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, alpha blockers, loop diuretics, thiazide diuretics, and centrally active antihypertensive medications. Statin users were defined as patients who filled prescriptions for

any of the following medications: atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin. Statin users may have been prescribed antihypertensive medication in addition to their cholesterol-lowering medication.

Several potential confounders were documented before or at the start of the observation period. Diabetes mellitus was coded present or absent in the analysis on the basis of the presence or absence of *ICD-9-CM* code, 250.XX, and a filled prescription for a medication from any of the following classes of medications: insulin, sulfonylurea, biguanide, thiazolidinedione, alpha-glucosidase inhibitor, and meglitinide. Cardiovascular disease was coded present or absent in the analysis on the basis of the presence or absence of *ICD-9-CM* codes, 410.XX–412.XX, 414.XX, 428.XX–438.XX, or 441.XX–444.2X. We defined aspirin use (yes or no) as an active prescription at the cohort entry date for any of the following agents: aspirin, aspirin buffered oral, aspirin oral enteric coated, and aspirin suppository. We defined finasteride use (yes or no) as an active prescription for finasteride at the cohort entry date. We defined PSA testing (yes or no) as having had a PSA test within 1 year before the cohort entry date and within the 2-year observation period. We defined having had a prostatectomy as the presence or absence of a surgical pathology report consistent with a prostatectomy after a diagnosis of prostate cancer. We extracted information from the electronic medical record on smoking history (yes, no, or unknown), age (years), weight (in kilograms), and height (in meters) at entry into the observation period. We identified measured serum values for TC, LDL-C, and HDL-C within 6 months before each patient's cohort entry date. We calculated non-HDL-C by subtracting HDL-C from TC among those patients who had both lipid parameters measured on the same day.

Statistical Analysis

We constructed age- and multivariable-adjusted Cox proportional hazard models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for prostate cancer incidence among statin users compared with the referent group, antihypertensive medication users. A Kaplan–Meier curve was created and reviewed to confirm the assumption of proportionality. Multivariable models for prostate cancer incidence among statin users compared with antihypertensive medication users included age, race, smoking history, prescription for aspirin, prescription for finasteride, PSA testing, diabetes mellitus, and total serum cholesterol. We also calculated a propensity score for being prescribed a statin using a logistic regression model with the same variables as listed above for the multivariable model. The c-statistic for the propensity score model was 0.79. We constructed models to predict prostate cancer incidence that included the propensity score among our entire cohort and the population within the fifth and 95th percentile of propensity score.

To further investigate the relationship between statin dose and prostate cancer incidence, we defined groups of patients by statin use within categories of equivalent simvastatin dosages, the most commonly used statin in our cohort (antihypertensive medication users, ≤10 mg equivalent simvastatin dose, 20 mg equivalent simvastatin dose, and ≥40 mg equivalent simvastatin dose) as previously described (12,13). Briefly, to allow time for a patient to achieve a stable statin dose, categories of equivalent simvastatin dosages were calculated on the basis of the dose and type of statin prescribed at 1 year after treatment initiation. Equivalent simvastatin dosages were calculated by dividing lovastatin and pravastatin doses by 2, dividing the fluvastatin dose by 4, and multiplying the atorvastatin dose by 2. We then determined the hazard ratio and 95% confidence interval of each tertile of equivalent simvastatin dose compared with our referent group for prostate cancer incidence. We controlled for the same potential confounders listed for our models described above. We calculated tests of trend across categories of equivalent simvastatin dose with the median dose in each category acting as an ordinal variable.

We also examined the relationship between serum lipid parameters at baseline and prostate cancer incidence. We constructed age- and multivariable-adjusted Cox proportional hazard models to calculate the hazard ratios and 95% confidence intervals for prostate cancer incidence by continuous measures and quartiles of each lipid parameter. Multivariable models contained all of the previously mentioned variables except that for each lipid parameter, the lipid parameter of interest was exchanged for TC. We calculated tests of trend across quartiles of each lipid parameter with the median value in each quartile acting as an ordinal variable. Quartiles of TC were defined as: <176, 176–206, 207–237, and > 237 mg/dL. Quartiles of HDL-C were defined as: <37, 37–42, 43–51, and >51 mg/dL. Quartiles of non-HDL-C were defined as: <131, 131–160, 161–192, and >192 mg/dL. Quartiles of LDL-C were defined as: <105, 105–131, 132–158, and >158 mg/dL. We created similar models to those listed above to examine the relationship between statin use and each lipid parameter with low- and high-grade prostate cancer incidence.

All statistical tests were two-sided and considered statistically significant if P is less than .05. Statistical tests were performed using SAS, version 9.1 (SAS, Cary, NC).

Results

We identified a cohort of 55 875 male patients who met our entry criteria. The mean age was 66.0 years (SD = 11.0 years) and median total follow-up time of 5.6 years (range = 2.0–11.0 years) in the overall cohort (median total follow-up time of 5.2 and 5.6 years was observed among antihypertensive medication users and statin users, respectively). The following is the proportion of each different statin agent in the statin user group 1 year after statin initiation: simvastatin, 54.6%; lovastatin, 43.9%; atorvastatin, 1.2%; pravastatin, 0.2%; and fluvastatin, 0.1%. The mean equivalent simvastatin dose among statin users was 26.2 mg (SD = 22.2 mg). Several characteristics of statin users and users of antihypertensive medications are presented in Table 1.

Among the referent group, 187 (1.3%) of 14 797 patients developed VA pathology-confirmed prostate cancer during their observation period compared with 359 (0.9%) of 41 078 patients taking statins. Overall, Gleason grade was reported in more than 99% of biopsy reports consistent with prostate cancer, and the most common total Gleason grade was 6 (Table 2).

Compared with patients taking antihypertensive medications, the risk of prostate cancer incidence was 31% less among patients taking statins (HR = 0.69, 95% CI = 0.52 to 0.90) after adjusting for age and other potential confounders (Table 3). Statin users

Table 1. Characteristics of patients taking an antihypertensive medication or statin (N = 55875)

Characteristic	Antihypertensive users (n = 14797)	Statin users (n = 41078)
Age, y		
Mean (SD)	65.2 (12.7)	66.3 (10.4)
Race, No. (%)		
White	7853 (53.1)	27319 (54.3)
Black	604 (4.1)	1007 (2.5)
Other	51 (0.3)	74 (0.2)
Missing	6289 (42.5)	17678 (43.0)
Smoker, No. (%)	3573 (24.2)	9039 (22.0)
Aspirin use, No. (%)	4310 (29.1)	15571 (37.9)
Finasteride use, No. (%)	1424 (9.6)	3733 (9.1)
Diabetes mellitus, No. (%)	1321 (8.9)	9299 (22.6)
Cardiovascular disease, No. (%)	4697 (31.7)	24469 (59.6)
Prostate-specific antigen test, No. (%)	6516 (44.0)	19131 (46.6)
Total cholesterol, mg/dL		
Mean (SD)	183.7 (35.4)	213.8 (47.8)
High-density lipoprotein cholesterol, mg/dL		
Mean (SD)	47.8 (15.1)	44.1 (11.2)
Non–high-density lipoprotein cholesterol, mg/dL		
Mean (SD)	136.4 (32.8)	168.7 (46.5)
Low-density lipoprotein cholesterol, mg/dL		
Mean (SD)	108.8 (28.8)	136.1 (39.1)

were 14% less likely (HR = 0.86, 95% CI = 0.62 to 1.20) to be diagnosed with low-grade prostate cancer and 60% less likely (HR = 0.40, 95% CI = 0.24 to 0.65) to be diagnosed with high-grade prostate cancer compared with use of antihypertensive medication. The trend for prostate cancer incidence across categories of equivalent simvastatin dose was non-statistically significant (slope = −0.01, P_{trend} = .09), but the risk of prostate cancer incidence was statistically significantly reduced in each category of equivalent simvastatin dose compared with patients taking antihypertensive medications. No apparent dose response among statin users compared with antihypertensive medication users was observed for low-grade prostate cancer incidence (slope = −0.00, P_{trend} = .83). However, for high-grade prostate cancer incidence, the trend across categories was statistically significant (slope = −0.03, P_{trend} = .005) and the risk in each category was statistically significantly reduced. Patients in the highest category of equivalent simvastatin dose were found to have a 73% decreased risk (HR = 0.27, 95% CI = 0.11 to 0.67) for high-grade prostate cancer compared with patients taking antihypertensive medications. Results from the overall cohort and between the fifth and 95th percentile of propensity score adjusted for the propensity score did not differ markedly from the results of our multivariable model (data not shown).

Table 2. Percentages of Gleason scores (N = 546)

Gleason score	Antihypertensive users No. (%)	Statin users No. (%)
2	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)
4	2 (1.1)	1 (0.3)
5	4 (2.1)	12 (3.3)
6	84 (44.9)	184 (51.3)
7 (3 + 4)	42 (22.5)	87 (24.2)
7 (4 + 3)	22 (11.8)	34 (9.5)
8	19 (10.2)	32 (8.9)
9	13 (7.0)	8 (2.2)
10	1 (0.5)	1 (0.3)

Increased levels of baseline TC appeared to increase the risk of total and high-grade prostate cancer incidence (Table 4). Every 10 mg/dL increase of baseline TC was associated with 2% increased risk of total prostate cancer (HR = 1.02, 95% CI = 1.00 to 1.05) and 6% increased risk of high-grade prostate cancer (HR = 1.06, 95% CI = 1.02 to 1.10). The highest quartile of TC at baseline was associated with a 45% increased risk of total prostate cancer (HR = 1.45, 95% CI = 1.07 to 1.97) and a 204% increased risk of high-grade prostate cancer (HR = 3.04, 95% CI = 1.65 to 5.60). TC was not associated with low-grade prostate cancer. Every 10 mg/dL increase of HDL-C at baseline was associated with 10% increased risk of total prostate cancer (HR = 1.10, 95% CI = 1.02 to 1.19) and 11% increased risk of low-grade prostate cancer (HR = 1.11, 95% CI = 1.02 to 1.21). The highest quartile of HDL-C at baseline was associated with a 45% increased risk of total prostate cancer (HR = 1.45, 95% CI = 1.08 to 1.95) and 157% increased risk of high-grade prostate cancer (HR = 2.57, 95% CI = 1.49 to 4.42). The highest quartile of LDL-C at baseline was associated with a 58% increased risk of total prostate cancer (HR = 1.58, 95% CI = 1.15 to 2.17) and 154% increased risk for high-grade prostate cancer (HR = 2.54, 95% CI = 1.34 to 4.81).

Discussion

Among patients in the New England VA Healthcare System, our study found that statin users were at lower risk for total and specifically high-grade prostate cancer incidence compared with users of antihypertensive medications. Furthermore, there was an inverse relationship between the dose of statin achieved at 1 year and the incidence of high-grade prostate cancer. We also found a strong direct relationship between baseline TC and total and high-grade prostate cancer. These findings are all consistent with the hypothesis that cholesterol plays an important role in total and high-grade prostate cancer incidence and medications that lower cholesterol, specifically statins, may reduce the risk of total and high-grade prostate cancer.

Previous observational studies have not clarified the relationship between statins and prostate cancer. Most of these studies only examined the relationship between statins and total prostate cancer and did not specifically investigate the relationship between statins and high-grade prostate cancer. Platz et al. (2) did examine the relationship between advanced prostate cancer patient statin use and metastasis and death and found a statistically significantly decreased risk for advanced prostate cancer among patients taking statins. To date, there are no reports of clinical trials of statins for prostate cancer prevention. One multicenter randomized placebo controlled clinical trial is examining the relationship between statins and prostate cancer biomarkers among men with Gleason

Table 3. Prostate cancer outcomes by use of antihypertensives, statins, and categories of equivalent simvastatin doses*

Outcome	Antihypertensive users	Statin users	Categories of equivalent simvastatin doses, mg			
			0	1–10	11–19	≥20
Total prostate cancer						
No. of patients	187	359	187	140	102	74
Person-years of follow-up	52 403	147 512	52 403	54 488	47 760	31 657
HR (95% CI)	1.0 (referent)†	0.69 (0.52 to 0.90)	1.0 (referent)	0.68 (0.51 to 0.89)	0.68 (0.50 to 0.92)	0.66 (0.46 to 0.95)
Low-grade prostate cancer‡						
No. of patients	132	284	132	113	78	60
Person-years of follow-up	52 257	147 313	52 257	54 398	47 689	31 631
HR (95% CI)	1.0 (referent)	0.86 (0.62 to 1.20)	1.0 (referent)	0.81 (0.58 to 1.12)	0.78 (0.55 to 1.12)	0.85 (0.57 to 1.29)
High-grade prostate cancer§						
No. of patients	55	75	55	27	24	14
Person-years of follow-up	52 403	147 512	52 403	54 488	47 760	31 657
HR (95% CI)	1.0 (referent)	0.40 (0.24 to 0.65)	1.0 (referent)	0.43 (0.25 to 0.74)	0.48 (0.26 to 0.86)	0.27 (0.11 to 0.67)

* Models were adjusted for the following variables: statin use (yes or no), finasteride use history (yes or no), age (years), serum total cholesterol (mg/dL), race (white, black, other, or missing), smoking history (yes or no), aspirin use (yes or no), heart disease (yes or no), diabetes mellitus (yes or no), history of prostate-specific antigen test (yes or no). CI = confidence interval; HR = hazard ratio.

† Referent defines the group that is the basis for the comparison.

‡ Low-grade prostate cancer is defined as a Gleason score ≤7 (3 + 4).

§ High-grade prostate cancer is defined as a Gleason score ≥7 (4 + 3).

grade 5 to 7 (3 + 4) prostate cancer who have been treated with a prostatectomy (14).

Measuring PSA has become the primary means of screening for prostate cancer incidence and progression. Several studies have found that men taking a statin may have a lower PSA (8,15,16). One explanation of our findings may be that decreased PSA levels secondary to taking a statin may have led to decreased PSA testing and therefore decreased incidence of prostate cancer. However, we found that more statin users had a PSA test than users of antihypertensive medications. If statin users were tested more frequently, perhaps another explanation of our results is lead-time bias. However, lead-time bias would result in a higher risk of low-grade prostate cancer among statin users. In fact, although non-statistically significant, we found statin users to be associated with a 14% reduced relative risk for low-grade prostate cancer.

One possible explanation for our findings could be a selection bias for cardiovascular disease that resulted in a difference in the competing risks between exposure groups. In our study, cardiovascular disease was more prevalent among statin users than antihypertensive users at baseline. Therefore, if statin users had more cardiovascular events and were not being tested for prostate cancer or died of cardiovascular events before being diagnosed for prostate cancer, statin users may have artificially appeared to be at lower risk for prostate cancer compared with antihypertensive medication users. However, we did not find any meaningful difference in the prevalence of PSA testing at baseline or follow-up time between exposure groups. Therefore, it is unlikely that the selection bias of cardiovascular disease would have resulted in a large enough difference in the competing risk of cardiovascular disease between exposure groups to explain our results.

Lipid rafts appear to be important for the development and progression of prostate cancer (17). Levels of caveolae have been associated with prostate cancer and aggressive prostate cancer (18). Caveolae are where HDL-C and the cell bind (19). Studies have shown that intracellular cholesterol plays a role in prostate cancer development and progression (20). However, to the best of our knowledge, few studies (10,21) have reported the relationship between various serum lipid parameters and prostate cancer incidence. It is interesting that we found a relationship between both serum TC and HDL-C, and high-grade prostate cancer, which was also independent of statin use.

One should consider several strengths and limitations when interpreting our findings. Our data are from the electronic medical records and administrative files of patients in the VA New England Healthcare System. Although we were able to identify when medications were prescribed, we were unable to confirm that patients actually took the medication. Also, we were unable to account for prescriptions of our medications of interest that occurred outside the VA Healthcare System. Furthermore, we were unable to identify patients with prostate cancer diagnosed outside the VA Healthcare System. However, among veterans eligible for VA health care, approximately 60% use a VA facility for their only source of primary care and approximately 20% use both a VA and a non-VA facility for their primary care (22). Because we required both exposure groups to be routine users of the VA Healthcare System, it is unlikely that there was nonrandom misclassification in either the receipt of medications of interest or diagnosis of prostate

Table 4. Prostate cancer outcomes by lipid parameters*

Outcome	Continuous	Quartiles of lipid parameters 1	2	3	4
Total cholesterol	10 units	<176 mg/dL	176–206 mg/dL	207–237 mg/dL	>237 mg/dL
Total prostate cancer					
No. of patients	349	72	86	81	110
Person-years of follow-up	112178	24985	27644	28404	31145
HR (95% CI)	1.02 (1.00 to 1.05)	1.0 (referent)†	1.13 (0.84 to 1.54)	1.16 (0.85 to 1.58)	1.45 (1.07 to 1.97)
Low-grade prostate cancer‡					
No. of patients	264	55	61	68	80
Person-years of follow-up	111939	24937	27569	28369	31064
HR (95% CI)	1.01 (0.98 to 1.04)	1.0 (referent)	0.99 (0.69 to 1.42)	1.10 (0.78 to 1.56)	1.14 (0.80 to 1.63)
High-grade prostate cancer§					
No. of patients	85	17	25	13	30
Person-years of follow-up	112178	24984	27644	28404	31145
HR (95% CI)	1.06 (1.02, 1.10)	1.0 (referent)	1.66 (0.93, 2.98)	1.27 (0.62, 2.59)	3.04 (1.65, 5.60)
HDL-cholesterol	10 units	<37 mg/dL	37–42 mg/dL	43–51 mg/dL	>51 mg/dL
Total prostate cancer					
No. of patients	313	69	65	87	92
Person-years of follow-up	97911	23641	24927	23489	25853
HR (95% CI)	1.10 (1.02 to 1.19)	1.0 (referent)	1.19 (0.85 to 1.65)	1.51 (1.13 to 2.02)	1.45 (1.08 to 1.95)
Low-grade prostate cancer					
No. of patients	239	55	47	70	67
Person-years of follow-up	97714	25815	23439	24875	23586
HR (95% CI)	1.11 (1.02 to 1.21)	1.0 (referent)	0.98 (0.66 to 1.44)	1.48 (1.07 to 2.05)	1.18 (0.83 to 1.68)
High-grade prostate cancer					
No. of patients	74	14	18	17	25
Person-years of follow-up	97911	25853	23489	24927	23641
HR (95% CI)	1.10 (0.94 to 1.28)	1.0 (referent)	2.11 (1.13 to 3.95)	1.56 (0.81 to 3.01)	2.57 (1.49 to 4.42)
Non-HDL-cholesterol	10 units	<131 mg/dL	131–160 mg/dL	161–192 mg/dL	>192 mg/dL
Total prostate cancer					
No. of patients	240	56	50	62	72
Person-years of follow-up	78250	17157	18774	19646	22672
HR (95% CI)	1.02 (0.99 to 1.05)	1.0 (referent)	0.94 (0.66 to 1.34)	1.30 (0.95 to 1.79)	1.13 (0.80 to 1.60)
Low-grade prostate cancer					
No. of patients	183	41	40	48	54
Person-years of follow-up	78105	17129	18734	19614	22628
HR (95% CI)	1.00 (0.96 to 1.04)	1.0 (referent)	1.02 (0.69 to 1.52)	1.21 (0.84 to 1.75)	1.00 (0.67 to 1.48)
High-grade prostate cancer					
No. of patients	57	15	10	14	18
Person-years of follow-up	78250	17157	18774.4	19646	22672
HR (95% CI)	1.06 (1.02 to 1.09)	1.0 (referent)	0.68 (0.29 to 1.58)	1.63 (0.86 to 3.10)	1.72 (0.86 to 3.46)
LDL-cholesterol	10 units	<105 mg/dL	105–131 mg/dL	132–158 mg/dL	>158 mg/dL
Total prostate cancer					
No. of patients	279	58	64	71	86
Person-years of follow-up	84068	17891	20083	21775	24320
HR (95% CI)	1.02 (0.98 to 1.05)	1.0 (referent)	1.27 (0.92 to 1.76)	1.41 (1.03 to 1.93)	1.58 (1.15 to 2.17)
Low-grade prostate cancer					

(Table continues)

Table 4 (Continued).

Outcome	Continuous	Quartiles of lipid parameters			
		1	2	3	4
No. of patients	215	41	52	59	63
Person-years of follow-up	83912	17856	20043	22 1748	24265
HR (95% CI)	1.01 (0.97 to 1.04)	1.0 (referent)	1.32 (0.92 to 1.90)	1.37 (0.96 to 1.95)	1.36 (0.94 to 1.97)
High-grade prostate cancer					
No. of patients	64	17	12	12	23
Person-years of follow-up	84068	17891	20083	21775	24320
HR (95% CI)	1.01 (0.95 to 1.08)	1.0 (referent)	1.09 (0.54 to 2.24)	1.53 (0.77 to 3.02)	2.54 (1.34 to 4.81)

* Multivariable models were adjusted for the following variables: statin use (yes or no), finasteride use history (yes or no), age (years), serum total cholesterol (mg/dL), race (white, black, other, or missing), smoking history (yes or no), aspirin use (yes or no), heart disease (yes or no), diabetes mellitus (yes or no), and history of prostate-specific antigen test (yes or no). CI = confidence interval; HDL = high-density lipoprotein; HR = hazard ration; LDL = low-density lipoprotein.

† Referent defines the group that is the basis for the comparison.

‡ Low-grade prostate cancer is defined as a Gleason score ≤7 (3 + 4).

§ High-grade prostate cancer is defined as a Gleason score ≥7 (4 + 3).

cancer outside the VA Healthcare System. We attempted to limit any healthy user bias by comparing statin users to patients with similar risk profiles, access to health care, and lifestyles. Because we compared statin users to users of antihypertensive medications and not the general population, care should be taken before extrapolating our results to the general population. Furthermore, antihypertensive medications have been hypothesized and investigated as risk factors for prostate cancer (23,24). If antihypertensive medications are associated with increased risk for prostate cancer, our results would likely overestimate the potential decreased risk of prostate cancer among patients taking statins. However, patients in both groups were taking antihypertensive medications. We relied on unconfirmed *ICD-9-CM* codes and pharmacy codes for identification of some of our potential confounders. Any misclassification of our confounders would likely be random and bias our results toward the null hypothesis. Although we did not have information on lifestyle variables such as diet and exercise, it is unlikely that any difference in lifestyle variables between users of statins or antihypertensive medications would be large enough to account for our statistically significant findings. Another limitation of our study is that quantitative information on smoking was not available from the medical records and patient files. Also, the lipid values used in the analysis were from a single time point, and therefore, no inferences on the relationship between change in lipid parameters and risk of prostate cancer incidence can be made. Because of the limited numbers of minorities in our veteran population, our results were not analyzed in terms of race.

In conclusion, men who use statins appear to be at lower risk for prostate cancer and specifically high-grade prostate cancer than men who use antihypertensive medications. Furthermore, men with higher levels of TC appear to be at higher risk of prostate cancer and specifically high-grade prostate cancer than men with lower levels of TC. Clinical trials should investigate whether statins may prevent prostate cancer and specifically high-grade prostate cancer.

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Funding

Research award W81XWH-08-2-0168 from the Department of Defense and grants 601 and 96 from the Cooperative Studies Program, Department of Veterans Affairs Office of Research and Development.

Notes

The study sponsors had no role in the collection, analysis, and interpretation of the data; the writing of the article; and the decision to submit the article for publication.

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Appendix 4: Published Paper from the Early Stage Prostate Cancer Cohort Titled, "The association between height and prostate cancer grade in the Early Stage Prostate Cancer Cohort Study."

Cancer Causes Control
DOI 10.1007/s10552-011-9820-x

ORIGINAL PAPER

The association between height and prostate cancer grade in the Early Stage Prostate Cancer Cohort Study

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Received: 21 September 2010 / Accepted: 5 July 2011

Abstract
Objective We examined the relationship between height and prostate cancer grade.
Methods The Early Stage Prostate Cancer Cohort Study is an observational cohort of 1,037 men diagnosed with early-stage prostate cancer, $T_{0-3}N_xM_0$. High-grade prostate cancer was defined as a biopsy Gleason score ≥ 7 (4 + 3). Logistic regression models were created to calculate odds ratios (OR) and 95% confidence intervals (CI) for the cross-sectional relationship between height and prostate cancer grade in the overall cohort and subpopulations.
Results We identified 939 participants with a biopsy Gleason score. High-grade prostate cancer was diagnosed in 138 participants. Overall, participants in the highest quartile of height were more than twice as likely to have a Gleason score ≥ 7 (4 + 3) than participants in the lowest quartile of height, OR 2.14 (95% CI 1.11, 4.14), after multivariate adjustment. Participants in the highest quartile of height were more likely to be diagnosed with high-grade prostate cancer than participants in the lowest quartile of height among participants who were black, OR 8.00 (95% CI 1.99, 32.18), and participants who had diabetes mellitus, OR 5.09 (95% CI 1.30, 19.98).
Conclusions Height is associated with increased risk of high-grade prostate cancer overall and perhaps among certain subpopulations.

Keywords Prostatic neoplasms · Body height · Epidemiology

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Introduction

Prostate cancer is a significant cause of morbidity and mortality among men. In 2010, it is estimated that 217,730 men were diagnosed with prostate cancer and 32,050 men died as a result of prostate cancer in the United States [1]. Given the large difference between the number of men who are diagnosed with prostate cancer and die from prostate cancer, it would be helpful to identify risk factors for prostate cancer that are more likely to lead to prostate cancer–related mortality. The pathologic grade of prostate cancer at diagnosis is related to the likelihood of prostate cancer mortality [2, 3].

Height is a potential risk factor for prostate cancer. A meta-analysis of 58 studies found that height was positively

Published online: 20 July 2011

associated with prostate cancer [4]. However, fewer studies have examined the relationship between height and advanced prostate cancer. Among the studies that have examined this relationship, taller men appear to be at higher risk for more advanced prostate cancer than shorter men [4–6] but not all studies have found this association [7, 8], and little is known about this relationship in subpopulations of men with different risks of prostate cancer. Therefore, we examined the relationship between height and prostate cancer grade in the Early Stage Prostate Cancer Cohort. Furthermore, we explored the relationship between height and prostate cancer grade in various subpopulations of men with potentially different risk of high-grade prostate cancer.

Materials and methods

Data sources

Men were eligible for participation in the Early Stage Prostate Cancer Cohort (ESPCC) study if they were diagnosed with early-stage prostate cancer, $T_{0–3}N_xM_0$, within two and a half years prior to enrollment. In addition, eligible men had no other history of cancer, with the exception of non-melanoma skin cancer, within 5 years of enrollment and had no other major illness that would have precluded long-term participation. Men with early-stage prostate cancer were identified at 16 sites throughout the VA Healthcare System.

A total of 1,037 men participated in the ESPCC study. Participants completed questionnaires at the initial interview that asked about demographic information including age, race, current weight, and current height; medical history including diabetes mellitus; and other potential risk factors for prostate cancer progression including smoking history and family history of prostate cancer. Questions were also asked about why prostate cancer had been suspected prior to a diagnosis.

Definition of outcome

The Gleason score was identified from pathology reports at the time of diagnosis and prostatectomies that had occurred by the time of the baseline survey. We identified Gleason scores from paper reports sent to us by site coordinators and using the Automated Retrieval Console [9] to review electronic reports in the VA Healthcare System electronic medical record. The appropriate Gleason score for each participant was selected according to the criteria of the 2005 International Society of Urological Pathology Consensus Conference on Gleason grading of prostatic carcinoma [10]. High-grade prostate cancer was defined as a Gleason score ≥ 8 as well as cases where the overall Gleason score was 7 and the primary score was ≥ 4.

Statistical analyses

We calculated the percent of men in our cohort with and without high-grade prostate cancer as well as the mean age, weight, and height $\pm$ standard deviation. We calculated the percent of men with a self-reported age at the time of prostate cancer diagnosis that matched $\pm$ 1 year their age identified in the electronic medical record, Veterans Affairs (VA) Patient Treatment File (PTF). We also calculated the percent of men who reported having diabetes mellitus and were found to have diabetes mellitus in the VA PTF at the time of prostate cancer diagnosis. We used logistic regression to examine the relationship between height as a continuous (5 cm) marker and grade of prostate cancer. Quartiles of height were defined, $<$172.7, 172.7–177.7, 177.8–182.7, and $>$182.7 cm. We used logistic regression to examine the relationship between quartiles of height and grade of prostate cancer with the lowest quartile as the referent quartile. We calculated the median height in each quartile and used logistic regression to calculate the p for trend across quartiles of height for prostate cancer grade. We performed age- and multivariate-adjusted models to calculate odds ratios (OR) and 95% confidence intervals (CI). Multivariate models controlled for age (years), race (white, black, other), family history of prostate cancer (yes, no, missing), whether the prostate cancer was suspected by PSA testing (yes, no), smoking status (no, current, quit), diabetes mellitus (yes, no), weight (kg), and site of enrollment (sites). We repeated the above procedures among groups stratified by the presence or absence of particular risk factors for high-grade prostate cancer. We dichotomized age and weight based upon the median values in the cohort. We limited the analysis to categories with $\geq$100 men and calculated the p value for the interaction term of each stratification. We also performed a sensitivity analysis among men who received a prostatectomy using height as a continuous (5 cm) marker and grade of prostate cancer at prostatectomy.

Results

Of the 1,037 participants in the ESPCC, we identified 939 with Gleason scores from biopsy pathology reports and 931 with Gleason scores and reported height. We found that the age at prostate cancer diagnosis that a participant reported and was identified in the VA PTF matched $\pm$ 1 year in 95% of the participants. We also found that a diagnosis of diabetes mellitus matched between participant's self-report and the VA PTF in 88% of participants. Overall, the mean $\pm$ standard deviation Gleason score from biopsy reports was 6.3 $\pm$ 1.1 units. The mean $\pm$ standard deviation height was 177.2 $\pm$ 7.1 cm. Taller participants were younger and heavier than shorter participants (Table 1). Taller participants

were more likely to be black and report a history of diabetes mellitus than shorter participants.

We identified 138 participants with a Gleason score ≥7 (4 + 3) at biopsy. Participants in the highest quartile of height were more than twice as likely to have a Gleason score ≥ 7 (4 + 3) at biopsy than participants in the lowest quartile of height, OR 2.14 (95% CI 1.11, 4.14), and the trend across quartiles was significant, p trend = 0.01, after multivariate adjustment (Table 2). Although not statistically significant, every 5-cm increase was associated with an increased risk for a Gleason score ≥ 7 (4 + 3) at biopsy, OR 1.11 (95% CI 0.96, 1.29). Among the 239 men who underwent prostatectomy, every 5-cm increase was also associated with an increased risk for a Gleason score ≥ 7 (4 + 3) at prostatectomy, OR 1.07 (95% CI 0.77, 1.48), although not statistically significant.

We examined the relationship between height and prostate cancer grade in various subpopulations (Table 3). Participants younger than age 65 years had a non-significant increased risk for a Gleason score ≥ 7 (4 + 3) with every 5 cm of height, OR 1.16 (0.90, 1.50), and the participants in the highest quartile of height were more likely, although not statistically significant, to have a Gleason score ≥ 7 (4 + 3) than participants in the lowest quartile of height, OR 4.06 (0.86, 19.15). Among black participants, every 5 cm of height was associated with an increased risk for a Gleason score of ≥ 7 (4 + 3) at biopsy, OR 1.44 (1.06, 1.95). Participants in the highest quartile of height were eight times more likely to have a Gleason score ≥ 7 (4 + 3) at biopsy than participants in the lowest quartile of height, OR 8.00 (1.99, 32.18), and the trend across quartiles was significant, p trend < 0.01. Among participants with diabetes mellitus, every 5 cm of height was associated with an increased risk for a Gleason score of ≥ 7 (4 + 3) at biopsy, OR 1.35 (1.00, 1.81). Participants in the highest quartile of height were over five times more likely to have a Gleason score ≥ 7 (4 + 3) at biopsy than participants in the lowest quartile of height, OR 5.09 (1.30, 19.98), and the trend across quartiles was significant, p trend = 0.01. Among participants who weighed < 87 kg, participants in the highest quartile of height were over three times more likely to have a Gleason score ≥ 7 (4 + 3) at biopsy than participants in the lowest quartile of height, OR 3.23 (1.24, 8.40), and the trend

Table 1 Participant characteristics by quartiles of height

Characteristics	Quartiles of height			
	<172.7 cm n = 196	172.7–177.7 cm n = 232	177.8–182.7 cm n = 261	>182.7 cm n = 242
Age, years, mean ± SD	65.9 ± 7.6	65.9 ± 7.9	65.3 ± 7.7	63.8 ± 7.6
Weight, kg, mean ± SD	81.1 ± 13.3	87.1 ± 17.0	91.1 ± 17.2	96.9 ± 17.5
Height, cm, mean ± SD	167.5 ± 3.2	174.0 ± 1.3	179.0 ± 1.3	186.0 ± 4.2
Race, %				
White	75.7	81.0	78.1	79.6
Black	23.3	18.2	21.5	20.0
Other	1.0	0.9	0.4	0.4
Family history of prostate cancer, %				
No	71.4	76.7	70.5	71.9
Yes	20.4	19.8	21.8	22.7
Missing	8.2	3.5	7.7	5.4
Suspected cancer due to PSA, %				
No	13.4	15.0	11.5	11.3
Yes	86.6	85.0	88.5	88.8
Smoke, %				
No	31.6	25.5	25.7	20.3
Current	15.0	20.8	16.9	19.1
Quit	53.4	53.7	57.5	60.6
Diabetes mellitus, %				
No	79.2	81.0	74.2	81.9
Yes	20.8	19.0	25.8	18.1
Received usual care in the VA Healthcare System, %				
No	9.0	11.2	10.1	7.1
Yes	91.0	88.8	89.9	92.9

Table 2 Odds ratios (95% confidence interval) of Gleason score ≥ 7 (4 + 3) compared with Gleason score ≤ 7 (3 + 4) at diagnostic biopsy by continuous height and quartiles of height in the overall cohort

	Continuous, 5 cm	Quartiles				*p*, trend
		< 172.7 cm	172.7–177.7 cm	177.8–182.7 cm	>182.7 cm	
Overall						
No. of cases	138	21	30	40	47	
Age-adj	1.15 (1.01, 1.31)	Referent	1.10 (0.61, 1.97)	1.42 (0.82, 2.48)	2.02 (1.17, 3.49)	<0.01
MV*-adj	1.11 (0.96, 1.29)	Referent	1.30 (0.67, 2.56)	1.61 (0.84, 3.08)	2.14 (1.11, 4.14)	0.01

* Multivariate model included the following covariates: age (years); race (white, black, other); family history of prostate cancer (yes, no, missing); prostate cancer suspected by PSA (yes, no); smoke (no, current, quit); diabetes mellitus (yes, no); weight (kg); site of enrollment (sites)

across quartiles was significant, p trend = 0.01. The p value for interaction was greater than 0.05 for each potential interaction.

Discussion

In the ESPCC, height appeared to be associated with increased risk of high-grade prostate cancer, Gleason score ≥ 7 (4 + 3), at biopsy. In the highest quartile of height, participants were more than twice as likely to have high-grade prostate cancer compared with the lowest quartile of height. In particular, among black participants and participants with diabetes mellitus, height was especially associated with a diagnosis of high-grade prostate cancer at biopsy.

Several potential mechanisms have been proposed for the relationship between height and prostate cancer. Insulin-like growth factor-I (IGF-I) has been found to be associated with body height in adolescence [11], and some [12, 13], but not all [14, 15], studies have found a relationship between height and levels of IGF-1 in adulthood. IGF-1 is known to be mitogenic and antiapoptotic [16], and it has been found to be positively associated with prostate cancer [17, 18]. Height has also been found to be genetically linked [19]. Therefore, genes that regulate height may also be associated with regulating prostate cancer development and progression.

IGF-1 levels may differ by age, race, and the presence or absence of diabetes mellitus. It is generally believed that levels of IGF-1 decline with increasing age [20]. McGreevy et al. reported that although plasma levels of IGF-1 were not different between black and white men, the level of IGF-binding protein-3 (IGFBP-3) and the ratio of IGF-1/IGFBP-3 were lower among black men [21]. This suggests that black men may have higher levels of bioavailable IGF-1. Although not all studies have found black men to have a lower ratio of IGF-1/IGFBP-3, several studies have found that black men have lower levels of IGFBP-3 [22–25]. Several cross-sectional studies have found elevated IGF-1 levels and decreased IGFBP-3 levels in patients with impaired glucose tolerance and diabetes mellitus [26, 27]; however, another study found decreased levels of IGF-1 among diabetic men compared with non-diabetic men [28].

One should consider several limitations of our analysis when interpreting our results. Our analysis is cross-sectional. Therefore, based upon our results, we cannot formally say that height is a risk factor for high-grade prostate cancer. However, it is difficult to imagine that high-grade prostate cancer affected a participant's height in this cohort of men with early-stage prostate cancer. Height was self-reported. However, the correlation between measured and self-reported height is typically high although shorter men tend to overreport their height more frequently than taller men [29]. This over reporting would tend to attenuate the effect of height on prostate cancer grade toward the null hypothesis. Furthermore, we had high correlation between self-reported age and diabetes mellitus and the values for these variables identified in the electronic medical record. This suggests that the height that participants reported was likely accurate. We had small numbers of men with high-grade prostate cancer and focused our analysis on Gleason scores obtained from biopsies rather than prostatectomy. However, we found consistent results whether we used Gleason scores obtained from biopsy or prostatectomy. We were unable to collect pathology reports from biopsies that occurred outside of the VA Healthcare System. However, we did not find a significant difference in the frequency of participants who reported that they received a majority of their care in the VA Healthcare System by quartiles of height. Our cohort was limited to men with early-stage prostate cancer. Therefore, our results are likely biased toward the null hypothesis and thus underestimate the true effect, since many cases of high-grade prostate cancer likely did not qualify for inclusion in the ESPCC. Although we found several apparent differences in the relationship between height and prostate cancer among various strata of risk factor groups for prostate cancer progression, none of the p values for interaction were significant. However, the interaction coefficient does not discern the balance of potential synergistic, antagonistic, or competitive relationships between variables and thus cannot rule out the presence of an interaction [30].

Table 3 Odds ratios (95% confidence interval) of Gleason score ≥ 7 (4 + 3) compared with Gleason score ≤ 7 (3 + 4) at diagnostic biopsy by continuous height and quartiles of height stratified by age, race, and presence or absence of diabetes mellitus

	Continuous, 5 cm	Quartiles				*p*, Trend	*p*, Interaction
		<172.7 cm	172.7–177.7 cm	177.8–182.7 cm	>182.7 cm		
Age							0.12
<65 years, $n = 429$							
No. of cases	47	4	9	14	20		
Age-adj	1.21 (0.98, 1.49)	Referent	2.07 (0.61, 7.00)	2.56 (0.81, 8.08)	3.45 (1.13, 0.49)	0.17	
MV*-adj	1.16 (0.90, 1.50)	Referent	2.95 (0.59, 14.66)	3.52 (0.74, 16.69)	4.06 (0.86, 19.15)	0.52	
≥65 years, $n = 498$							
No. of cases	90	17	20	26	27		
Age-adj	1.12 (0.96, 1.32)	Referent	0.96 (0.48, 1.94)	1.29 (0.66, 2.53)	1.90 (0.96, 3.75)	<0.01	
MV*-adj	1.10 (0.92, 1.32)	Referent	1.06 (0.49, 2.33)	1.32 (0.62, 2.83)	1.96 (0.90, 4.29)	0.01	
Weight							0.48
<87 kg, $n = 455$							
No. of cases	58	13	16	15	14		
Age-adj	1.15 (0.94, 1.41)	Referent	1.11 (0.51, 2.45)	1.47 (0.66, 3.25)	2.28 (1.00, 5.20)	0.02	
MV*-adj	1.21 (0.96, 1.52)	Referent	1.56 (0.65, 3.73)	1.70 (0.69, 4.18)	3.23 (1.24, 8.40)	0.01	
≥87 kg, $n = 471$							
No. of cases, $n = 471$	79	7	14	25	33		
Age-adj	1.11 (0.93, 1.33)	Referent	1.39 (0.53, 3.70)	1.62 (0.66, 3.99)	2.13 (0.88, 5.18)	0.09	
MV*-adj	1.08 (0.88, 1.31)	Referent	1.02 (0.33, 3.08)	1.49 (0.55, 4.07)	1.70 (0.63, 4.61)	0.27	
Race							0.19
White, $n = 727$							
No. of cases	96	14	23	31	28		
Age-adj	1.08 (0.92, 1.26)	Referent	1.31 (0.65, 3.80)	1.72 (0.88, 3.37)	1.71 (0.86, 3.41)	0.04	
MV*-adj	1.03 (0.86, 1.23)	Referent	1.21 (0.56, 2.62)	1.65 (0.79, 3.46)	1.47 (0.67, 3.20)	0.14	
Black, $n = 191$							
No. of cases	40	6	6	9	19		
Age-adj	1.37 (1.07, 1.75)	Referent	1.03 (0.28, 3.80)	1.42 (0.45, 4.51)	5.29 (1.78, 15.77)	<0.01	
MV*-adj	1.44 (1.06, 1.95)	Referent	1.40 (0.31, 6.23)	1.56 (0.37, 6.61)	8.00 (1.99, 32.18)	<0.01	
Family history of prostate cancer							0.56
No, $n = 676$							
No. of cases	104	15	23	32	34		
Age-adj	1.21 (1.03, 1.42)	Referent	1.21 (0.60, 2.44)	1.88 (0.96, 3.66)	2.35 (1.21, 4.59)	<0.01	
MV*-adj	1.14 (0.94, 1.37)	Referent	1.24 (0.57, 2.69)	1.73 (0.81, 3.70)	2.00 (0.92, 4.35)	0.07	

Table 3 continued

	Continuous, 5 cm	Quartiles				*p*, Trend	*p*, Interaction
		<172.7 cm	172.7–177.7 cm	177.8–182.7 cm	>182.7 cm		
Yes, $n = 198$							
No. of cases	27	5	6	5	11		
Age-adj	1.08 (0.83, 1.39)	Referent	0.86 (0.23, 3.22)	0.67 (0.18, 2.49)	1.71 (0.54, 5.39)	0.19	
MV*-adj	1.09 (0.81, 1.47)	Referent	0.87 (0.18, 4.23)	0.80 (0.19, 3.49)	1.90 (0.47, 7.74)	0.22	
Suspected cancer due to PSA							0.82
No, $n = 117$							
No. of cases	17	3	6	3	5		
Age-adj	1.16 (0.80, 1.70)	Referent	1.57 (0.34, 7.16)	0.88 (0.16, 4.86)	1.79 (0.37, 8.57)	0.75	
MV*-adj	1.13 (0.74, 1.72)	Referent	3.04 (0.44, 21.09)	1.41 (0.18, 11.04)	2.27 (0.34, 15.03)	0.80	
Yes, $n = 804$							
No. of cases	120	18	23	37	42		
Age-adj	1.15 (1.00, 1.32)	Referent	1.09 (0.56, 2.11)	1.63 (0.89, 2.98)	2.24 (1.23, 4.09)	<0.01	
MV*-adj	1.10 (0.94, 1.29)	Referent	1.16 (0.56, 2.42)	1.66 (0.83, 3.31)	2.12 (1.04, 4.38)	0.01	
Smoke							0.81
No, $n = 236$							
No. of cases	34	6	3	13	12		
Age-adj	1.27 (1.00, 1.61)	Referent	0.43 (0.10, 1.85)	1.93 (0.67, 5.55)	3.32 (1.12, 9.86)	0.01	
MV*-adj	1.19 (0.89, 1.59)	Referent	0.33 (0.06, 1.81)	1.21 (0.31, 4.74)	2.71 (0.67, 11.0)	0.07	
Current or previous, $n = 690$							
No. of cases	104	15	27	27	35		
Age-adj	1.09 (0.94, 1.28)	Referent	1.43 (0.72, 2.83)	1.34 (0.68, 2.63)	1.88 (0.98, 3.64)	0.05	
MV*-adj	1.07 (1.03, 1.15)	Referent	1.53 (0.72, 3.23)	1.49 (0.70, 3.17)	1.89 (0.89, 4.04)	0.07	
Diabetes mellitus							0.12
No, $n = 724$							
No. of cases	98	16	22	31	29		
Age-adj	1.07 (0.92, 1.25)	Referent	1.00 (0.51, 1.94)	1.53 (0.82, 2.87)	1.45 (0.77, 2.74)	0.09	
MV*-adj	1.02 (0.86, 1.22)	Referent	1.33 (0.62, 2.84)	1.74 (0.83, 3.66)	1.55 (0.71, 3.34)	0.22	
Yes, $n = 193$							
No. of cases	38	5	7	9	17		
Age-adj	1.35 (1.05, 1.75)	Referent	1.34 (0.36, 4.93)	1.13 (0.35, 3.71)	4.61 (1.48, 14.42)	<0.01	
MV*-adj	1.35 (1.00, 1.81)	Referent	1.23 (0.28, 5.39)	1.51 (0.39, 5.84)	5.09 (1.30, 19.98)	0.01	

* Multivariate models included each of the following covariates except for the categorical variable by which the population was stratified: age (years); race (white, black, other); family history of prostate cancer (yes, no, missing); prostate cancer suspected by PSA (yes, no); smoke (no, current, quit); diabetes mellitus (yes, no); weight (kg); site of enrollment (sites)

Conclusions

In the ESPCC, height appeared to be associated with increased risk of high-grade prostate cancer, especially among younger participants, black participants, and participants with diabetes mellitus. Future research should focus on the relationship between height and prostate cancer mortality as well as the potential mechanism for the specific relationship between height and prostate cancer grade among younger men, black men, and men with diabetes mellitus.

Acknowledgments Supported by research award W81XWH-08-2-0168 from the Department of Defense and grants 601 and 96 from the Cooperative Studies Program, Department of Veterans Affairs Office of Research and Development.

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Appendix 5: IRB Approval

Department of Veteran Affairs	REPORT OF SUBCOMMITTEE ON HUMAN STUDIES

PROJECT/PROGRAM TITLE: 2P. Request for **Continued Approval** of Human Studies IRB #2140 "The Relationship between Statins and Prostate Cancer Prevention"

PRINCIPAL INVESTIGATOR: Wildon Farwell, M.D.

VAMC:	REVIEW DATE:
VA Boston Healthcare System	**February 28, 2011**

COMMITTEE FINDINGS:

1. The information given in the Informed Consent under the Description of Research by Investigator is complete, accurate, and understandable to a research subject or a surrogate who possesses standard reading and comprehension skills.
   - ☐ YES
   - ☐ NO
   - ☒ ICF Waived

2. The informed consent is obtained by the principal investigator or a trained and supervised designate under suitable circumstances.
   - ☐ YES
   - ☐ NO
   - ☒ ICF Waived

3. Every effort has been made to decrease risk to subject(s)?
   - ☒ YES
   - ☐ NO

4. The potential research benefits justify the risk to subject(s)?
   - ☒ YES
   - ☐ NO

5. If subject is incompetent and surrogate consent is obtained, have all of the following conditions been met; a) the research can't be done on competent subjects; b) there is no risk to the subject, or if risk exists the direct benefit to subject is substantially greater; c) if an incompetent subject resists, he will not have to participate; d) if there exists any question about the subject's competency, the basis for decision on competency has been fully described.
   - ☐ YES
   - ☐ NO
   - ☒ ICF Waived

6. If the subject is paid the payment is reasonable and commensurate with the subject's contribution.
   - ☐ YES
   - ☐ NO
   - ☒ Not enrolling

7. Members of minorities and women have been included in the study population whenever possible and scientifically desirable.
   - ☐ YES
   - ☐ NO
   - ☒ Not enrolling

8. Comments: (Indicate if Expedited Review)
This study continues to meet the criteria for waiver of the requirement of informed consent. This study continues to meet the criteria for waiver of HIPAA authorization.

RECOMMENDATION: ☒ APPROVE ☐ DISAPPROVE / REVISE

SIGNATURE OF CHAIRMAN	DATE:
Carole Palumbo, Ph.D. Chair, Human Studies Subcommittee	**February 28, 2011**

VA BOSTON HEALTHCARE SYSTEM

HUMAN STUDIES SUBCOMMITTEE (IRB)

REPORT OF COMMITTEE ACTION

Version December 1, 2004

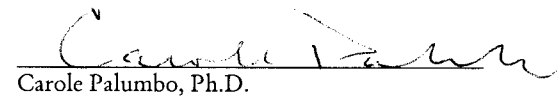
Date of Action:	February 28, 2011
Principal Investigator:	Wildon Farwell, M.D.
Title of Submission:	"The Relationship between Statins and Prostate Cancer Prevention"
Protocol Number:	IRB #2140
Type of Submission & Item Description:	Request for Continued Approval of Human Studies.
Human Subject Enrollment:	Yes: X No:
Vulnerable Population:	Yes: No: X Category: Entire Study: Sub-Population:
Sponsor:	DoD
Administrator of Funding:	BVARI

X	APPROVED at IRB meeting
	APPROVED under procedures for expedited review by
	CHANGES REQUIRED: Based on Committee review, the changes or actions noted below are stipulated as required for approval. Compliance with these stipulations may be confirmed under Committee procedures for expedited review.
	DEFERRED: The item has been deferred pending changes or clarifications noted below. The proposal will be reconsidered at the next Committee meeting after the requested information or changes are submitted.
	DISAPPROVED: The proposal was disapproved for the reasons noted below. Please consult with the ACOS for Research or the Committee Chairperson before resubmitting.
	NOTED

Note: For 'Changes Required' and 'deferred', responses must be received from the principal investigator within 60 days. After 60 days a new submission and full review are required.

COMMENTS (2P):

1. The IRB determined that no conflict of interest for the PI or any other study personnel that may influence the conduct of the research existed previously for this protocol or arose since the last continuing review.
2. This study continues to meet the criteria for waiver of the requirement for informed consent under 38 CFR 16.116(d)
3. This study continues to meet the criteria for waiver of HIPAA authorization under 45 CFR 164.512(i)(2)
4. This study has been designated as minimal risk and one year approval.
5. Approval dates: 2/28/11 - 2/27/12.
6. The IRB determined that future 'Requests for Continuing Review' qualify for approval under expedited review procedures.
7. Additional requirements for Department of Defense studies have been met.



Carole Palumbo, Ph.D.
Chair, Human Studies Subcommittee